I.—A RESEARCH INTO THE PRODUCTION, LIFE AND DEATH OF CRESCENTS IN MALIGNANT TERTIAN MALARIA, IN TREATED AND UNTREATED CASES, BY AN ENUMERATIVE METHOD

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PREFATORY NOTE.

This research has been carried on in the Tropical Ward of the Royal Southern Hospital, Liverpool, under the direction of Major Ronald Ross, C.B., F.R.S., and is a continuation of the research described in a former paper (Ross and Thomson [1910]). The funds were supplied by the Advisory Committee of the Colonial Office. The work has been facilitated by a new instrument, which enables one to estimate the number of parasites, leucocytes, etc., in a given volume of blood by a method based on Ross's 'Thick Film Process' [1903]. A following paper will describe this instrument and the method of its use.

INTRODUCTION

Knowledge regarding 'Crescents,' or the sexual forms of the malignant tertian malarial parasite (*Plasmodium falciparum*), is of considerable importance owing to the fact that mosquitos are infected by them, and thereby transmit the disease from man to man. As is well known, there are three distinct stages in the life history of the malarial parasite, namely (1) the stage of asexual parasites (fever forms); (2) the stage of sexual parasites or gametes; and (3) the stage of the parasite in mosquitos.

All these stages are essential for the spread of malaria, so that by dealing successfully with any one stage the disease can no longer be propagated, and must therefore dwindle and die.

It is, however, the second stage (sexual stage) of the parasite that I wish to consider. Less is known concerning it than of the first and second periods. No one can demonstrate how the sexual forms are produced, nor how long they live; and no effective method of killing them has been found. Research regarding this obscure stage is therefore necessary, and of great importance. When we know how to destroy the sexual malarial parasites, or how to prevent their production, we will have another powerful weapon whereby we can exterminate the disease. In this article I shall call the sexual parasites 'crescents,' as I have dealt only with cases of *P. falciparum*. The accompanying table has been compiled from the cases studied by the enumerative method used in this research. Some of the results have already been mentioned in the previous paper referred to above.

THE PRODUCTION OF CRESCENTS

From the figures given regarding the forty-two cases of *P. falciparum* studied, it is clearly noticeable that the production of crescents is extremely irregular. Certain paroxysms of fever result in a numerous brood of crescents even up to 7,000 per c.mm. of the patient's blood. Other paroxysms produce very few or none at all. Thirty-one, or 74 per cent. of the cases, showed crescents at some time during the period of examination. Eleven, or 26 per cent., showed no crescents at any time while under observation.

A. How are Crescents produced and where are they developed? All malarial experts seem agreed that the crescents are developed from the ordinary asexual spores or merozoits of the parasite.

Mannaberg [1894] stated his belief that they were produced from the conjugation of two asexual parasites within a red corpuscle. If this is so, then the more numerous these asexual forms are, the greater is the likelihood of two or more finding their way into a red cell, that is according to the theory of probability. In Case 13 where there were 300,000 asexual parasites per c.mm. of blood, many of the red cells contained more than one parasite. In Case 18 asexual parasites were few and difficult to find (1,860 per c.mm.), and no doubly infected corpuscles could be detected; yet

in the former case no crescents were produced, whereas in the latter, 286 crescents per c.mm. of blood appeared. Again, as shown in Table A, the cases with very numerous asexual parasites produced on the average fewer crescents than cases with much less numerous asexual parasites. These facts would appear to bring strong evidence against Mannaberg's hypothesis. The following quotation is from Stephens and Christophers [1908]:—'The sexual cycle, it has been thought, commences in the blood when the conditions are unfavourable for the continuance of the asexual cycle, and, in fact, has been taken as a sign that the patient has already developed immunity against the fever-producing young parasites (spores). Thus it is well known that in malignant tertian the sexual forms, gametes or crescents, first appear a week to ten days after the first febrile attack. If this view be true, then it follows that the gametes develop from forms already present in the system, viz., the asexual forms, and possibly the divergence into sexual forms takes place from the youngest form of the parasite, i.e., the spore. But it is possible that the divergence takes place at a stage previous to the youngest form of the parasite, i.e., at a stage immediately preceding the entry of the sporozoits into the blood, so that we have from the first indifferent and sexual forms present, involving indeed the existence of three kinds of sporozoits. Sexual development has been supposed to proceed mainly in the internal organs, e.g., the bone marrow, but it is being gradually recognised that young forms of gametes are also found in the circulation.'

This research would appear to support the idea that the crescents are developed from the asexual spores when a certain amount of immunity has developed, but it seems to me that they do not come from special asexual spores, but that they arise merely owing to a transformation of an ordinary asexual spore into a sexual parasite. I will give evidence to show that the development of immunity is necessary for their production, and I fail to see why, if they do develop from special spores they cannot be produced at any time independently of immunity. There seems to be little doubt also that they develop chiefly in the internal organs, and when completely developed they appear suddenly in the peripheral blood; for, although small undersized crescents are sometimes seen, yet their occurrence in the peripheral blood is rare. I have never seen

in the peripheral blood anything which could be considered as an intermediate stage between an asexual spore and a true crescent.

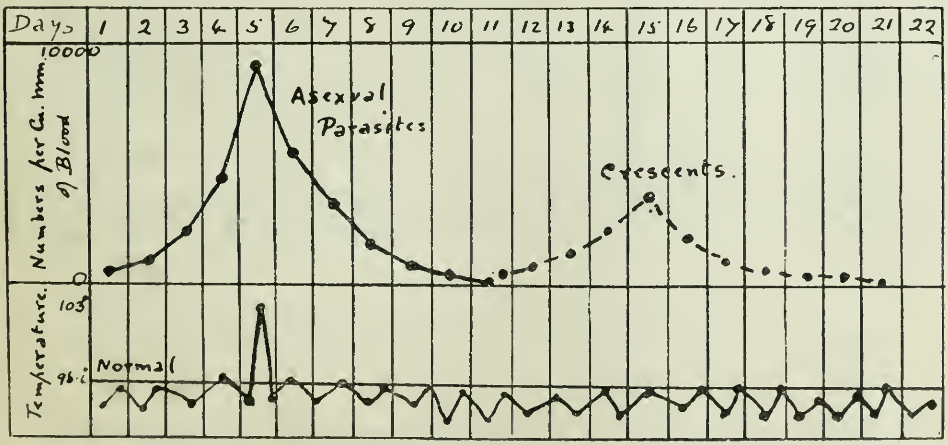
B. When are Crescents produced? The accumulated evidence of the crescent cases studied seems to show that a period of ten days elapses between the appearance in the peripheral blood of the asexual spores, and the crescents which are produced from these spores. As a general rule the crescents appear in the peripheral blood on the fifth day after the attack of fever, and increase in number for four or five more days, so that they are most numerous on about the tenth day after the height of the fever. Those crescents appearing on the fifth day after the paroxysm correspond to asexual parasites existing in the blood five days previous to this paroxysm. Asexual parasites can exist in the blood in numbers as great as 2,000 and rarely 10,000 per c.mm. without producing any temperature reaction. They gradually increase in number by sporulation till they are numerous enough to cause a paroxysm of fever. The numbers may then fall spontaneously or by quinine treatment so that only one single paroxysm results. It is by the study of such single paroxysms that the time required for the appearance in the peripheral blood of the corresponding crescents can be best determined. In such cases the graphs representing the numbers of asexual parasites and crescents show a striking similarity, the points on the crescent graph occurring on the tenth day after the corresponding points on the graph of the asexual parasites. It is very difficult to demonstrate this with mathematical accuracy, and very frequent examinations of the blood require to be made.

The chart of Case 20 shows the correspondence fairly well. A careful study of all the charts leads one to the conclusion that the corresponding points on the crescent curve occur about ten days after those of the asexual curve. This conclusion is strengthened by the chart of Case 38. In this case the numbers of leucocytes, crescents and asexual parasites were estimated several times daily for twenty-three days.

This case is extremely interesting, as the patient had nine successive daily paroxysms of fever. Four paroxysms on the four days before admission, and five paroxysms on the next five days. Corresponding to these nine fever paroxysms or sporulations we

have nine outbursts of crescents into the peripheral circulation, each occurring on the tenth day after the corresponding fever paroxysm. The asexual parasites were rapidly destroyed by quinine after the ninth paroxysm of fever, and a corresponding diminution in the production of crescents is evident ten days later. It is stated in the above quotation from Stephens and Christophers that many have observed the appearance of crescents on the eighth to the tenth day after the first paroxysm of fever, but this delay is attributed to the development of immunity, whereas it is due to the fact that crescents take that time to develop from the asexual spores before they appear in the peripheral circulation. The following diagrammatic charts A and B represent the correspondence between asexual parasites and the crescents developed therefrom, where only one blood count is made per day.

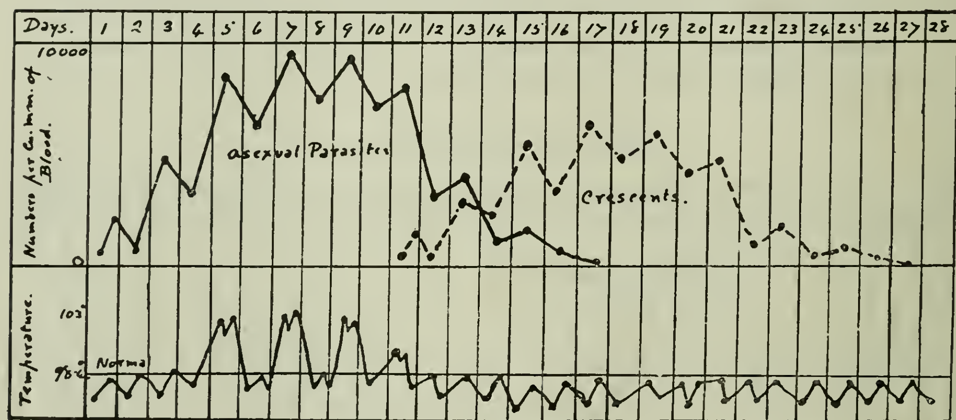
Diagram A. (Single fever paroxysm.)



C. Why are Crescents produced in some Cases and not in others? Crescents would seem to be developed from the asexual spores, due to a development of immunity towards the latter. When the asexual spores find that their environment is becoming unsuitable, they undergo a transformation into a sexual generation and thereby save themselves from destruction. In this new state they remain passive, waiting for their transference into a more suitable host. Schaudinn and other observers have stated that

they have seen sexual gametes undergoing a change back into asexual spores by parthenogenesis. Although this has never been observed by workers in the Liverpool School of Tropical Medicine, yet in the light of the above theory it would seem quite possible that such a retransformation might take place, especially in cases where the acquired immunity had become less or disappeared. This phenomenon must, however, be very rare, as it would otherwise have been noticed more often.

DIAGRAM B. (Showing tertian paroxysms with corresponding outbursts of crescents ten days later.)



The following evidence would seem to supply seven points in support of the statement that crescents are formed after the development of partial immunity.

(1) *The relationship between the number of asexual parasites and the number of crescents produced.* Taking very acute cases, I find that out of eight paroxysms of fever caused by numbers of asexual parasites over 50,000 per c.mm. of blood, only three, or 37·5 per cent. resulted in crescent production. A total of 724,000 asexual parasites per c.mm. produced a total of 1,354 crescents per c.mm., giving a ratio of 535 asexual parasites to one crescent.

Eleven subacute paroxysms had asexual parasites varying from 20,000 to 50,000 per c.mm. of blood; of these, seven, or 63·6 per cent., resulted in crescent formation. A total of 318,700 asexual

parasites per c.mm. produced a total of 3,952 crescents per c.mm. of blood, giving a ratio of 81 asexual parasites to one crescent.

Twenty-six mild chronic cases had asexual parasites, varying from 1,100 to 20,000 per c.mm. of blood. Eighteen of these, or 69·25 per cent., resulted in crescent production. A total of 172,360 asexual parasites per c.mm. produced a total of 3,343 crescents per c.mm. of blood, giving a ratio of 52 asexual parasites to one crescent.

The mild, chronic, and probably partially immune cases had therefore a crescent-producing power fully ten times greater than the very acute cases.

(2) *The duration of the disease in relation to the production of crescents.* Sixteen paroxysms occurred during the first thirty days of the disease. Of these 43·7 per cent. produced crescents. The total average number of crescents was 161 per c.mm. of blood.

Twenty paroxysms occurred between the thirtieth and the sixtieth day of the disease. Of these 65 per cent. produced crescents, the total average number of crescents being 551 per c.mm.

Sixteen paroxysms occurred after the sixtieth day of the disease. Twelve, or 75 per cent. of these produced crescents, and the total average number of crescents was 650 per c.mm. of blood.

Thus it would appear that crescents are more likely to be produced in cases of long standing, where a certain amount of immunity has had time to develop.

(3) *Crescent production in cases which have had previous attacks of fever one or more years previously.* Sixteen cases had had previous attacks of fever. Of these, 87 per cent. developed crescents during the period of observation. There were twenty-six cases which had no history of previous attacks; of these, only 46 per cent. produced crescents. It is reasonable to suppose that these cases, which had a history of previous attacks, were more immune than the primary cases.

(4) *The relationship between crescent production and the age of the patient.* From the table it can be seen that 50 per cent. of the cases up to twenty years of age (average eighteen years) produced crescents, the average number being 130 per c.mm. of blood.

Cases between twenty and thirty years of age (average twenty-six years) gave an average of 526 crescents per c.mm., 74 per cent. of the paroxysms resulting in crescents.

Cases between thirty and sixty-eight years of age (average forty-five years) gave an average of 1,018 crescents, 71 per cent. of the paroxysms producing crescents.

There is apparently an increase in crescent-producing power in older patients. This might be attributed to a greater power in adults of developing immunity, as compared with the young growing patients. Many of the older patients, however, had been in the tropics for a long time, and had had previous attacks of fever. The young patients had not been long in malarial districts, and in most cases it was their first attack of malaria. The greater crescent-producing power in the older patients may therefore have been due to immunity developed from previous attacks.

(5) *The relationship between crescent production and the percentage of the patient's haemoglobin.* Nineteen paroxysms of fever, occurring chiefly in different cases where the haemoglobin during the next ten days was 75 per cent. and under, produced only an average of twenty-two crescents per c.mm. of blood. Of these paroxysms, 52 per cent. produced crescents.

Twenty-seven paroxysms, where the haemoglobin during the next ten days was over 75 per cent., produced an average of 428 crescents per c.mm., and nineteen, or 70 per cent., of these paroxysms produced crescents.

It would seem therefore that a low percentage of haemoglobin is not so favourable for crescent production as a fairly high percentage. This again might be explained by the supposition that immunity to the asexual parasites is more likely to be successfully developed in cases where the blood standard is fairly healthy.

(6) *Crescent production in relation to the size of the spleen.* Twenty-six cases had palpable spleens. Of these, fifteen, or 75 per cent., produced crescents. In twenty-three cases the spleen could not be palpated. Twelve, or 52 per cent. of these produced crescents.

According to Ross [1910] the number of asexual parasites tends to vary inversely as the degree of splenomegaly, that is, the parasites tend to die out in persons with very large spleens. Again, N. F. Surveyor [1910] states that malignant malaria is more fatal in cases where the spleen is not enlarged, and less fatal in those with splenomegaly. These statements would seem to indicate that immunity to the disease increases *pari passu* with the size of the spleen; hence the increased crescent production where the spleen is enlarged.

(7) *Crescent production in relation to the number of leucocytes.* The average number of leucocytes in the ten-day periods following paroxysms which produced no crescents was 7,284 per c.mm. of blood (56 per cent. mononuclears). After paroxysms producing up to 100 crescents per c.mm., the average number of leucocytes during the same period was 7,411 per c.mm. (52 per cent. mononuclears). While after paroxysms producing over 100 crescents per c.mm., the average number of leucocytes was 8,924 per c.mm. (53 per cent. total mononuclears).

Again in thirteen cases, which produced no crescents at any time, the average number of leucocytes throughout was 8,646 per c.mm. (total mononuclears 55·9 per cent.), as compared with an average of 10,970 per c.mm. (total mononuclears 48·9 per cent.), in sixteen cases with numerous crescents throughout the period of examination.

It would appear therefore, that greater numbers of crescents are produced in cases where the leucocytes are numerous.

The leucocytes in malaria increase markedly in number, simultaneously with the quiescence of the disease. About one week after the last paroxysm of fever, the leucopenia (characteristic as a rule of the febrile period in malaria) disappears, and a leucocytosis takes its place, provided the fever does not return. Thus a high leucocyte count is characteristic of quiescent malaria and in post-malarial conditions, and would appear to be coincident with periods of immunity. This increase in the number of peripheral blood leucocytes occurs after the fever abates, whether quinine has been given or not. Where quinine is given, it occurs earlier and remains permanent, because during the treatment no true relapse

can occur. The leucocytes decrease in number previous to the onset of a relapse. The chart of Case 20 shows the fall in the number of leucocytes with the onset of a relapse, and later an increase in crescent production when the leucocyte count again becomes high. These facts would tend to show that a high leucocyte count and immunity are co-existent, the latter explaining the increase of crescents.

(8) *Crescent production in relation to the month of infection.* We have not sufficient cases on record to make any reliable deductions. We can only state, that from West Africa, cases infected in all months of the year except June produced crescents, and again cases infected in every month, except May and July, showed no production of crescents. From this evidence there seems no reason to suspect that crescent production depends upon the month of infection.

D. The Effect of Quinine on Crescent Production*. It would appear that quinine in doses of ten grains three times daily, given just before and during the paroxysm of fever, diminishes the subsequent formation of crescents. The cases showing the greatest numbers of crescents had little or no quinine for several days previous to the producing paroxysm, and little or no quinine during that paroxysm. Case 23 seems to show the good effects of quinine in this respect. In this case the first paroxysm of fever produced 852 crescents per c.mm. of blood, resulting from 50,000 asexual spores per c.mm. Twenty grains of quinine were given during this paroxysm, but none was given for several days before or after it. The next relapse where no quinine was given till the day after the paroxysm produced 468 crescents per c.mm., while the next paroxysm of this relapse produced 344 crescents per c.mm. from 54,000 fever forms per c.mm. During this last paroxysm and afterwards thirty grains of quinine was given daily. A subsequent relapse treated similarly with quinine gave a production of only four crescents per c.mm. from fever forms amounting to 16,000 per c.mm. of blood. This case and others would seem to indicate that if quinine is given in doses of ten grains three times daily during

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* The various salts of quinine used were kindly supplied by Messrs. Burroughs, Wellcome & Co.

the fever paroxysm and afterwards, it helps much to prevent the formation of crescents. The destructive action of quinine in these doses on the asexual spores is so powerful and rapid that one is surprised at the subsequent appearance of even a few crescents. If quinine is withheld till one or two days after the fever paroxysm and then given in the above daily doses, the crescents may still appear in large numbers—*vide* Cases 20, 22, etc. This shows that when once the crescents have commenced to develop, the quinine does not then prevent them from reaching maturity and appearing in the peripheral blood on the tenth day or thereabout. I would therefore conclude that quinine in large daily doses, given during and after the fever paroxysm, diminishes the crescent-producing power of that paroxysm, not by acting on the crescents themselves, but indirectly by destroying the asexual spores from which the crescents are produced. However, if quinine be given in smaller doses, say five grains daily, or ten to twenty grains irregularly, then instead of the crescent production becoming less, there is evidence to show that it may become even more prolific. Thus in Case 18, crescents became much more numerous after quinine was administered in daily doses of five grains. This case with such treatment showed a very high crescent-producing power, the ratio of asexual spores to crescents being as eight is to one approximately. It is quite reasonable to suppose that in such cases, quinine given in small doses destroys only some of the asexual spores, but enables the host to keep the disease under control, and to develop some resistance or immunity. In the consequence more crescents develop from the remaining parasites. Case 18 and others showed the presence of asexual parasites for many days during the administration of quinine in doses of five grains daily.

Quinine given continuously in daily doses of twenty to thirty grains, has never failed in our cases to reduce the crescents to numbers less than one per c.mm. of blood in a period not exceeding three weeks, vide chart of Case 49. This reduction of crescents by quinine has also been noted by Darling [1910].

E. The effect of Methylene Blue on Crescents. It would appear from the careful investigation of six cases treated alone with methylene blue, that this drug in doses of twelve grains daily, given by mouth (pill form), though not so potent in destroying

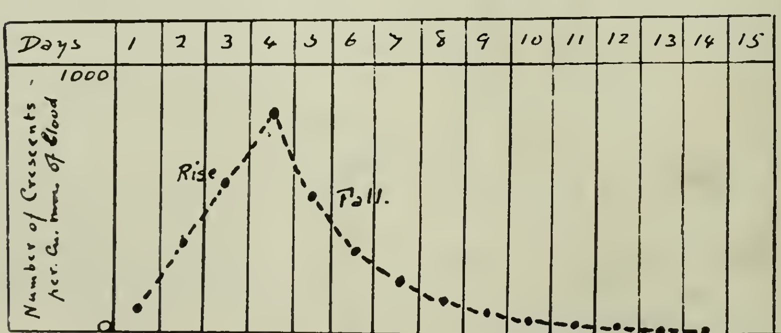
the asexual parasites, is yet more potent than quinine in preventing crescent formation. It would seem also to have some direct destructive effect on the crescents. It is good treatment, therefore, to give methylene blue along with quinine, especially where one cannot give large doses of the latter due to the idiosyncrasy of the patient.

THE DURATION OF LIFE, AND THE DEATH OF CRESCENTS

(*a*) *There is evidence to show that the duration of life of a crescent cannot be more than twenty days.* During the first ten days of this period they are developing somewhere, but not in the peripheral blood. They then appear in the peripheral blood, sometimes small in size. The majority of them must perish in the peripheral blood in a very few days. This must be so, for if they lived for say four days or longer, then the summit of the crescent curve would not be a sharp point as it always is, especially when the numbers are great.

(*b*) *The appearance of the graph, representing the life and death of crescents in the peripheral blood.* The crescent curve has a definite formation. Where the number of crescents is estimated only once daily, it assumes more or less the appearance shown in the diagram C.

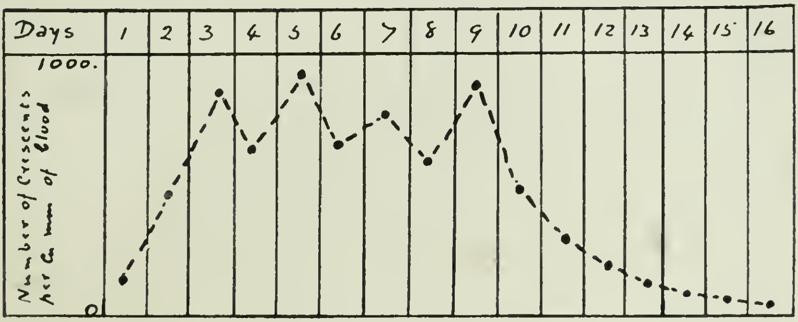
DIAGRAM C. (Crescent curve, numbers estimated once daily.)



This is the usual type of crescent curve obtained after a single isolated paroxysm of fever, where the number of crescents is estimated once daily. When no quinine is given, a single isolated paroxysm is rare, and the crescent curve will as a rule be quite

different, as in Cases 1, 14, 16, 18, 23, 24, etc. In these cases the number of crescents remains high for some days, the graph resembling a kind of plateau containing several sharp peaks, as in diagram D.

DIAGRAM D. (Crescent curve with plateau formation.)



The explanation of this plateau is quite simple, for if no quinine is given the asexual parasites remain alive, even though there is no fever to indicate their presence, and keep on producing new crescents. The source of crescents is not cut off, so that the supply is replenished by new broods of crescents, appearing every day, or on alternate days, or irregularly, according as the fever or asexual sporulation occurs every day, on alternate days, or irregularly. The sharp peaks on the plateau of the curve show that although the crescents are dying rapidly, yet their numbers are replenished by fresh broods coming into the circulation. As pointed out by Ross and Thomson [1910], these peaks on the crescent curve often show a tertian tendency.

In no case is there a plateau formed when quinine has been given in doses of thirty grains daily ten days previous to the height of the crescent curve. If a plateau has formed and quinine is then administered in large doses, its effect will not be manifested for about ten days, because although it very quickly reduces the source of supply, yet those crescents which commenced to develop during the previous ten days are not affected, but continue to appear in the peripheral blood replenishing the loss. Thus quinine, as is clearly seen in Case 23, takes about ten days to destroy the plateau formation. Hence, though quinine makes the crescents disappear from the peripheral blood more quickly than they would otherwise

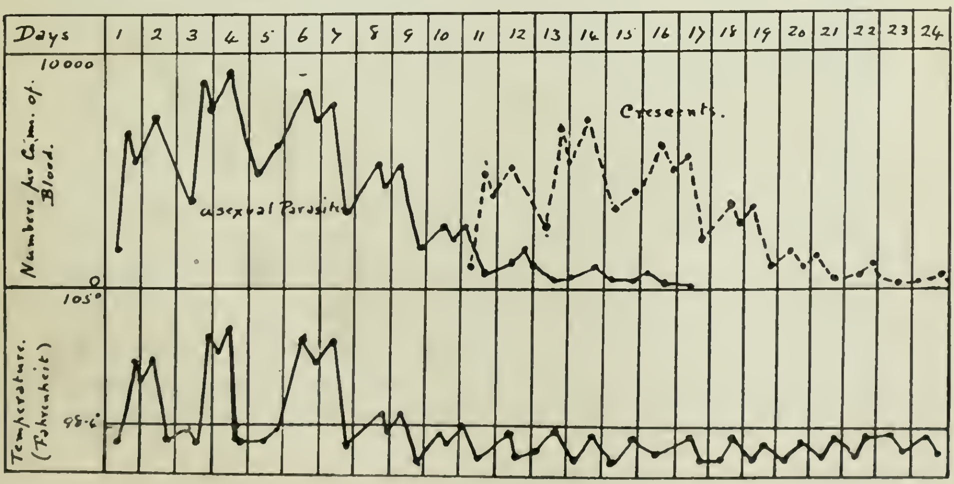
do without its administration, yet this effect is not due to any direct destructive action on the crescents themselves. It is due indirectly to the destruction of the asexual spores from which the crescents are developed. The length of time that crescents will remain in the peripheral blood therefore depends upon the persistence of the asexual parasites. If immunity develops so strongly that the asexual parasites almost disappear, or if they are destroyed by quinine, then the crescents also will disappear in due course.

In cases where immunity remains, but is only sufficient to keep the number of asexual parasites in check, crescents may continue almost indefinitely. Crescents have been observed to continue in the peripheral blood for eight weeks, Surveyor [1910]. Case 18, where the asexual source of supply was not destroyed by quinine till late, had crescents for forty-four days, and probably longer than this, as they were present when the case first came under our observation. Sufficient has been said to point out the fallacies regarding the duration of life of crescents. I must, however, once more refer to the chart of Case 38. Here the number of crescents per c.mm. of blood was estimated several times daily. The crescent graph obtained shows the great importance of making numerous observations, for had the numbers been estimated only once a day, the daily variation in the number of crescents would not have been noticed. Here we have a pure quotidian case of fever, resulting in quotidian outbursts of crescents into the peripheral circulation, each crescent outburst corresponding to a sporulation of the asexual parasites occurring ten days before. It is noticeable that the quinine in doses of thirty grains daily did not appreciably diminish the numbers of crescents till the tenth day after its administration. The number of crescents then diminished, rapidly at first and afterwards more slowly, for nine more days. This would seem to indicate that the quinine quickly destroyed the majority of the parasites of the asexual source, the remainder dying more slowly. The curve also clearly shows that the crescents die very quickly in the peripheral blood stream; a very marked fall occurs each day, but this fall is compensated for by a fresh brood each day. It is clear that but for this compensation the crescents would only remain in the peripheral blood for a very few days. Again it will be observed that although asexual parasites could no

longer be detected in the blood after the third day of quinine, yet crescents continued to be present till the eighteenth day of quinine treatment. Thus those crescents found after thirteen days of quinine administration had either a life of five days in the peripheral blood, or else they were new crescents produced from surviving asexual spores, so few in number that they could not be detected. When quinine has been given in the above doses for a few days asexual parasites can no longer be found, but the fact that relapses occur (even when there are no crescents), shows that they were still present. They may exist in numbers below the detectable limit, or (?) as resisting forms in the internal organs, and it is possible the crescents found more than thirteen days after the administration of quinine come from these.

In other cases, where the number of crescents was estimated several times daily, the graph obtained was much more irregular than in Case 38. In these, daily irregular variations took place, vide chart of case 49. This is easily explained, for in many cases of malignant tertian, sporulation is extremely irregular. It is very seldom that one gets so well a defined quotidian sporulation as in Case 38. In cases of malignant tertian therefore with irregular temperature indicating irregular sporulation, one would expect the crescent graph, as estimated from several counts daily, to be irregular also. The majority of our cases have shown this irregularity. The following diagrammatic chart will indicate the idea more clearly.

DIAGRAM E. (Represents a pure tertian fever or sporulation.)



This chart represents the true relationship between crescents and the asexual spores in a pure case of malignant tertian fever. A case with an irregular fever, indicating irregular sporulations, would give an irregular crescent graph. These points, however, still require to be worked out more thoroughly.

There is, however, one very constant law regarding the crescent graph, viz., that the curve representing the diminution or death rate of the crescents is always a parabolic line (vide curve shown in Diagram C). This shape of curve arises from the fact that they die off by a constant fraction, say one-half to one-fifth of their daily number. One might give two explanations of this law regarding their death rate.

(1) That it is a case of the survival of the fit, a certain proportion dying day by day according to their varying powers of resistance.

(2) That it depends upon the law of probability regarding their contact with leucocytes, by which they are ingested. The mononuclear leucocytes, especially the large forms, undoubtedly ingest crescents, either when alive or after their death, for in cases where only numerous crescents are present in the blood, many pigmented mononuclear leucocytes are to be found. It is quite reasonable to suppose that there may be some truth in these two hypotheses, but I think the true explanation is to be found by studying the curve of the asexual forms from which the cresents arise. It is clearly seen from the charts of Cases 17, 38, and others, that the curve representing the death rate of the asexual parasites is also a parabolic line, as shown diagrammatically in Chart A. The curve is the same, whether they die off spontaneously or under the influence of quinine. Now, when the producers of crescents show this death rate curve, and if the crescents produced have approximately all the same duration of life, then necessarily the curve of their death rate which will occur ten days later will assume the same form. Hence the peculiar form of the crescent curve depends probably in every respect upon the form of the curve of the asexual parasites. The form of the asexual parasite curve most probably depends in its turn upon (1) The law of the survival of the fit; (2) The law of probability of leucocyte contact and ingestion. The large mononuclears undoubtedly ingest the asexual parasites, especially the spores. When the spores are

numerous many will be ingested, but as they become fewer the chance of contact and ingestion by these leucocytes will become less.

CONCLUSIONS REGARDING PROPHYLAXIS

From the above research one might give the following deductions regarding the prevention of malaria:—

(*a*) It is a bad practice to give quinine in small doses of five grains daily, or irregularly, even though the doses be larger, for such treatment tends to increase the power of crescent formation.

(*b*) All cases of malaria should be treated early and continuously with doses of quinine of about twenty to thirty grains daily, as such treatment during and after the fever diminishes the subsequent formation of crescents. Continuous treatment with the above doses has never failed, as stated above, to reduce the number of crescents to less than one per c.mm. of blood in a period not exceeding three weeks. That is to say, it renders infective cases of malaria non-infective to mosquitos in a period not exceeding three weeks.

SUMMARY

1. Crescents are produced from the ordinary asexual spores of *P. falciparum*, due to a development of immunity towards the latter.

2. They develop somewhere in the internal organs and then appear suddenly in the peripheral blood.

3. The period required for their development is about ten days.

4. Crescents do not generally live more than a few days in the peripheral blood.

5. Crescents may be present in the peripheral blood during periods as long as eight weeks, not because the individual crescents survive for that time, but because their numbers are constantly replenished from surviving asexual forms.

6. Fresh broods of crescents come into the circulating blood daily, or every other day, or irregularly, according as the asexual sporulations occurring ten days before were quotidian, tertian, or irregular.

7. Quinine has no direct destructive action on crescents, either during their development or afterwards, but it destroys the asexual source of supply.

8. Quinine reduces the crescents to numbers less than one per c.mm. of blood within three weeks, provided it be given in daily doses of twenty to thirty grains.

9. Quinine in small doses tends to increase crescent production (?) by favouring the development of immunity to the asexual parasites.

10. Methylene blue in doses of twelve grains daily reduces the number of crescents, and would seem to have some direct destructive action upon them.

LITERATURE

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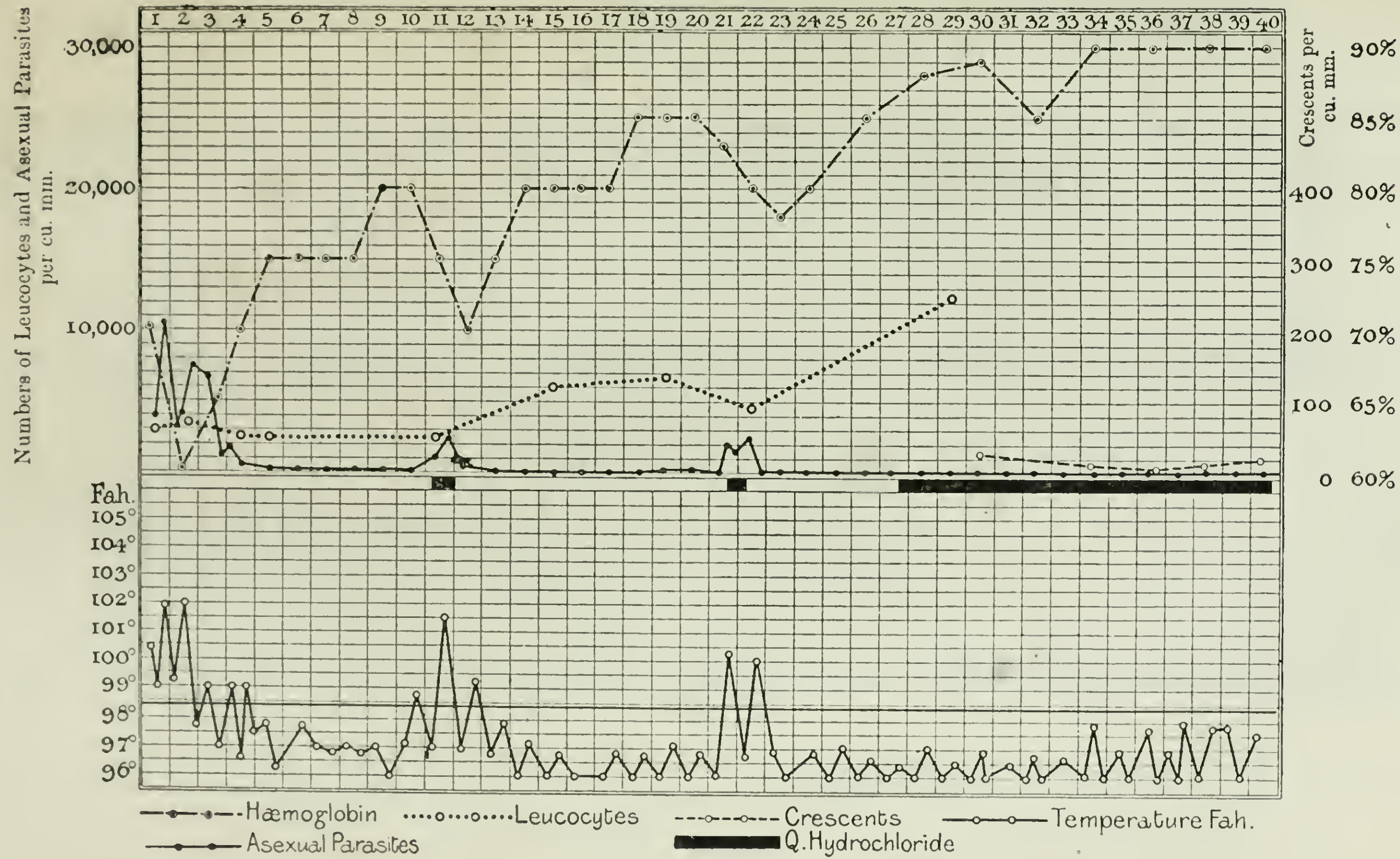
TABLE A

Case	Age	Where infected	Month of infection	Duration of disease up to fever paroxysm	Quinine previous to fever paroxysm	Maximum asexual parasites per c.mm. during fever paroxysm	Maximum Cresents per c.mm. produced	Day of maximum Cresent production	Average haemoglobin % during the 10-day period	Average leucocytes per c.mm. during the 10-day period	Average total mono-nuclear percentage during the 10-day period	Average daily quinine for 10-day period	Average daily methylene blue for 10-day period	Total duration of Cresents in days
				days								grains	grains	
10	37	Kamerun, W. A.	September	140	Nil for 3 days	15,000 ?	10	—	—	5,500	—	4	Nil	?
1	42	Niger, W.A.	November	70	Little ?	??	220	—	—	2,900	50·5	Nil	7	over 22
11	17	Niger, W.A.	January	190	Nil for 14 days	64,000 ?	0	—	—	5,600	51	30	Nil	?
12	24	Niger, W.A.	December	30	Nil for 3 days	50,000	34	10th	—	6,910	51	13	Nil	over 13
13	22	Congo	December	30	70 grains in 30 days	300,000	0	—	—	11,400	55	27	0	—
14	31	Gold Coast	November	63	Nil for several weeks	37,000 ?	1,500	—	—	7,070	43	3	0·9	Over 18
15	27	Vera Cruz	November	49	Quinine irregularly	?	7,000	—	—	12,000	54	?	0	Over 12
16	17	Niger, W.A.	September	70	Little	?	244	—	—	10,310	69	0	x c.c. polychrome blue	Over 28
17	19	Congo	January	49	Nil for 14 days	10,000	0	—	72	2,375	69	0	0	—
17 Relapse	19	Congo	January	59	Nil for 25 days	3,000	0	—	80	5,620	51	2	0	—
17 Relapse	19	Congo	January	69	Nil for 10 days	2,500	25	10th	83	8,280	44·7	15	0	—
18	29	Congo	January	77	Nil for 50 days	1,860	286	8–12th	84	9,830	54·5	4·5	0	Over 43
19	20	Niger, W.A.	February	40	Very little	5,240	0	—	72	4,300	46·6	2	0	—
20	24	Niger, W.A.	February	40	Very little	7,400	16	9th	72	5,890	39·6	3	0	33
20 Relapse	24	Niger, W.A.	February	60	Nil for 16 days	4,000	88	10th	68	4,140	—	28	0	33
21	50	Niger, W.A.	March	28	250 grains	36,000	4	—	66	4,400	—	11	0	17
22	30	Niger, W.A.	March	40	Nil for 4 days	7,920 ?	1,388	10th	80	11,550	—	22	0	31
22—2nd Parox.	30	Niger, W.A.	March	42	Nil for 6 days	45,000 ?	1,240	9–10th	78	8,850	—	30	0	31
23	17	Niger, W.A.	March	21	Nil for 14 days	50,000	852	10th	80	4,360	56	3	0	32
23 Relapse	17	Niger, W.A.	March	30	Nil for 8 days	34,000	468	9–10th	77	6,440	59	23	0	32
23 Relapse	17	Niger, W.A.	March	32	Nil for 10 days	54,000	344	10th	79	5,950	59	23	0	32
23 Relapse	17	Niger, W.A.	March	46	Nil for 7 days	16,700	4	—	82	7,780	—	30	0	32
24	29	Niger, W.A.	March	28	Nil for 9 days	25,000	572	10th	76	8,420	—	2	0	35
24 Relapse	29	Niger, W.A.	March	34	Nil for 5 days	9,500	630	10th	78	8,570	—	1	0	35
24 Relapse	29	Niger, W.A.	March	46	Nil for 9 days	4,000	68	—	79	5,500	—	22	0	35

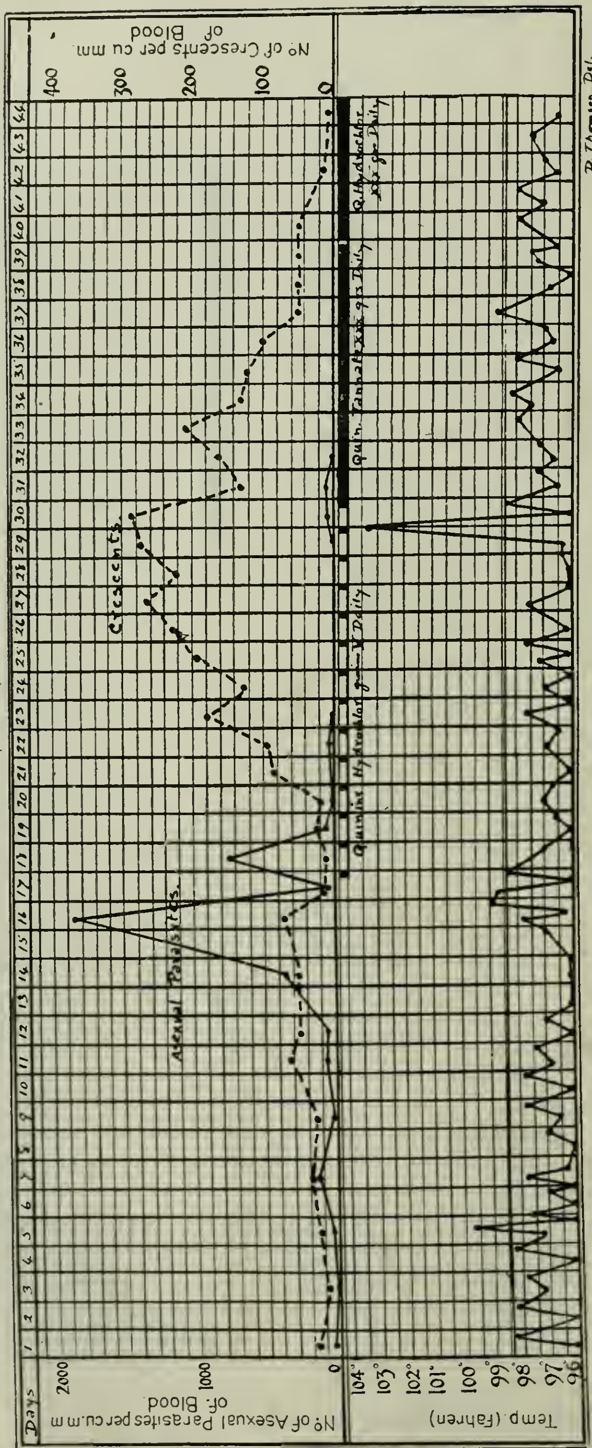
Table A—continued.

Case	Age	Where infected	Month of infection	Duration of disease up to fever paroxysm	Quinine previous to fever paroxysm	Maximum asexual parasites per c.mm. during fever paroxysm	Maximum Cresents per c.mm. produced	Day of maximum Cresent production	Average haemoglobin % during the 10-day period	Average leucocytes per c.mm. during the 10-day period	Average total mononuclear percentage during the 10-day period	Average daily quinine for 10-day period	Average daily methylene blue for 10-day period	Total duration of Cresents in days
				days								grains	grains	
24 Relapse	29	Niger, W.A.	March	49	Nil for 10 days	15,000	28	—	82	6,580	—	30	0	3;
25	20	Gambia	March	23	Nil for 6 days	22,000	0	—	77	8,200	—	27	0	—
26	44	Niger, W.A.	April	20	Little	9,700	0	—	85	10,540	—	10	0	—
26 Relapse	44	Niger, W.A.	April	27	Nil for 7 days	2,000	0	—	88	15,650	—	30	0	—
27	30	W.A.	May ?	?	Nil for weeks	1,104	8	—	74	12,320	—	0	0	Over 4
28	25	Niger, W.A.	April	42	Nil for 7 days	3,040	0	—	87	8,190	58	9	0	—
29	38	Niger, W.A.	April	70	Nil for 2 days	6,500	4	—	63	7,940	61	25	0	—
30	53	Niger, W.A.	May	15	A little	4,000	152	9th	90	8,940	57	1	0	Over 12
31	20	Niger, W.A.	March	90	10 grains daily for 10 days	28,000	0	—	75	5,170	59·3	0	10	—
32	20	W.A.	February ?	150	Nil for long time	few	244	—	76	11,710	60	0	0	Over 7
33	18	W.A.	June	10	?	6,700	0	—	99	7,410	57·5	14	0	—
34	23	W.A.	August	63	Nil for 3 weeks	84,400	0	—	69	6,159	50	27	0	—
35	16	W.A.	October	14	Nil for 7 days	70,000	0	—	34	8,540	52	20	0	—
36	38	W.A.	October	9	Little	50,000	0	—	80	3,200	62	25·5	0	—
37	26	W.A.	September	21	Nil for 5 days	29,000	0	—	78	10,040	77·3	19·5	0	—
38	25	W.A.	July	91	Very Little	26,900	144	10th	80	11,350	38·5	16·5	0	22
39	40	W.A.	September	70	Nil for 6 days	22,000	24	10th	49	5,830	57	26	0	Over 11
40	19	W.A.	September	24	Nil	21,800	0	—	62	9,240	80, only one count	0	12	—
41	24	Southern U.S.A.	October	49	Nil for 2 days	20,000	0	—	45	5,450	45·2	10·5	11	Over 5
41 Relapse	24	Southern U.S.A.	October	54	Nil for 6 days	12,000	0	—	50	6,050	43	17	12	Over 5
42	28	U.S.A.	October	49	Nil for 21 days	7,000	48	9th	58	10,820	45	0	0	Over 20
43	22	W.A.	August	21	Nil for 3 weeks	6,000	500	—	93	10,600	49·5	22	0	Over 16
44	26	W.A.	September	42	Nil for 5 days	5,400	32	9th	79	7,800	—	30	0	Over 13
45	62	W.A.	June	140	Nil for 3 days	5,000	0	—	43	5,270	—	17	0	—
46	26	W.A.	August	42	35 grains in a week	3,000	24	—	88	13,050	—	4	0	13
47	17	W.A.	August	35	Nil	2,000	8	—	69	7,610	—	11	9	15
48	18	W.A.	July	70	?	1,800	32	10th	64	5,640	67·5	19·5	0	Over 6
49	68	Rangoon	Sept. ?	49 ?	Little	?	4,450	—	83	16,170	45	?	0	Over 23
50	45	Bombay	October	65 ?	Some irregularly	?	7,688	—	—	5,610	44	?	10 grains daily	Over 20
51	38	W.A.	?	?	?	?	200	—	40	—	—	—	—	—

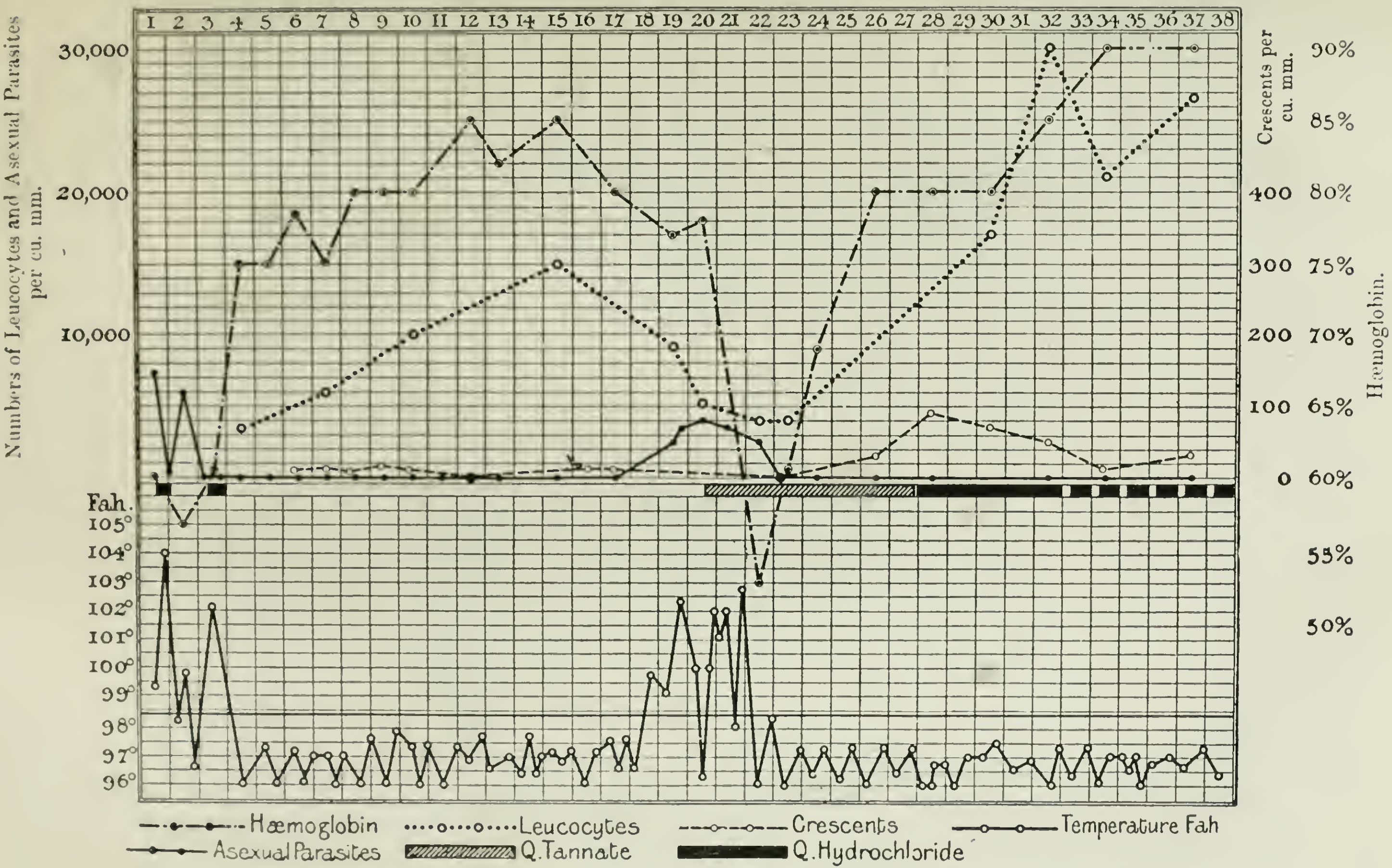
CASE 17.—R.B. *P. falciparum.*



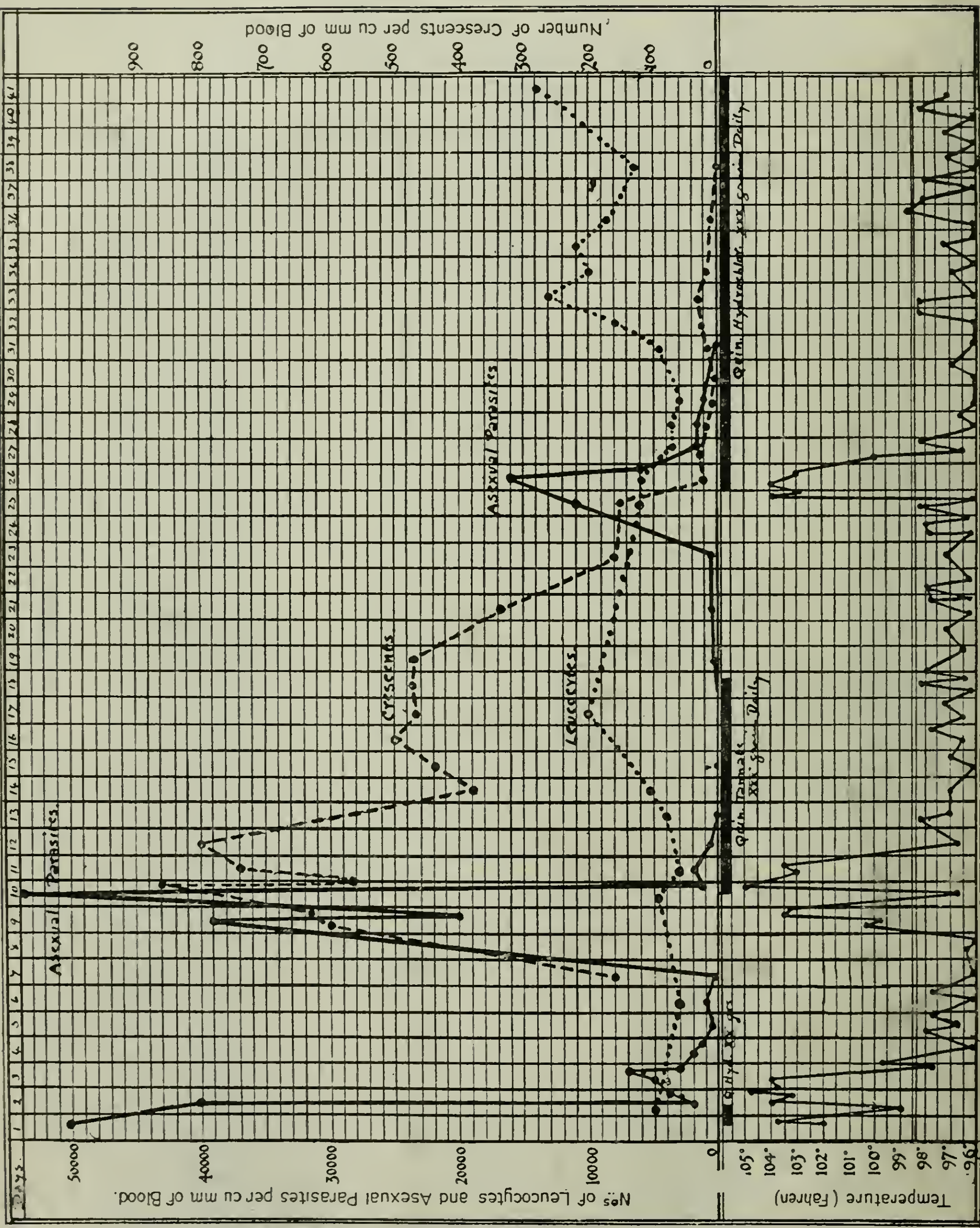
A.C. Case 18. (P.Falciparum.)

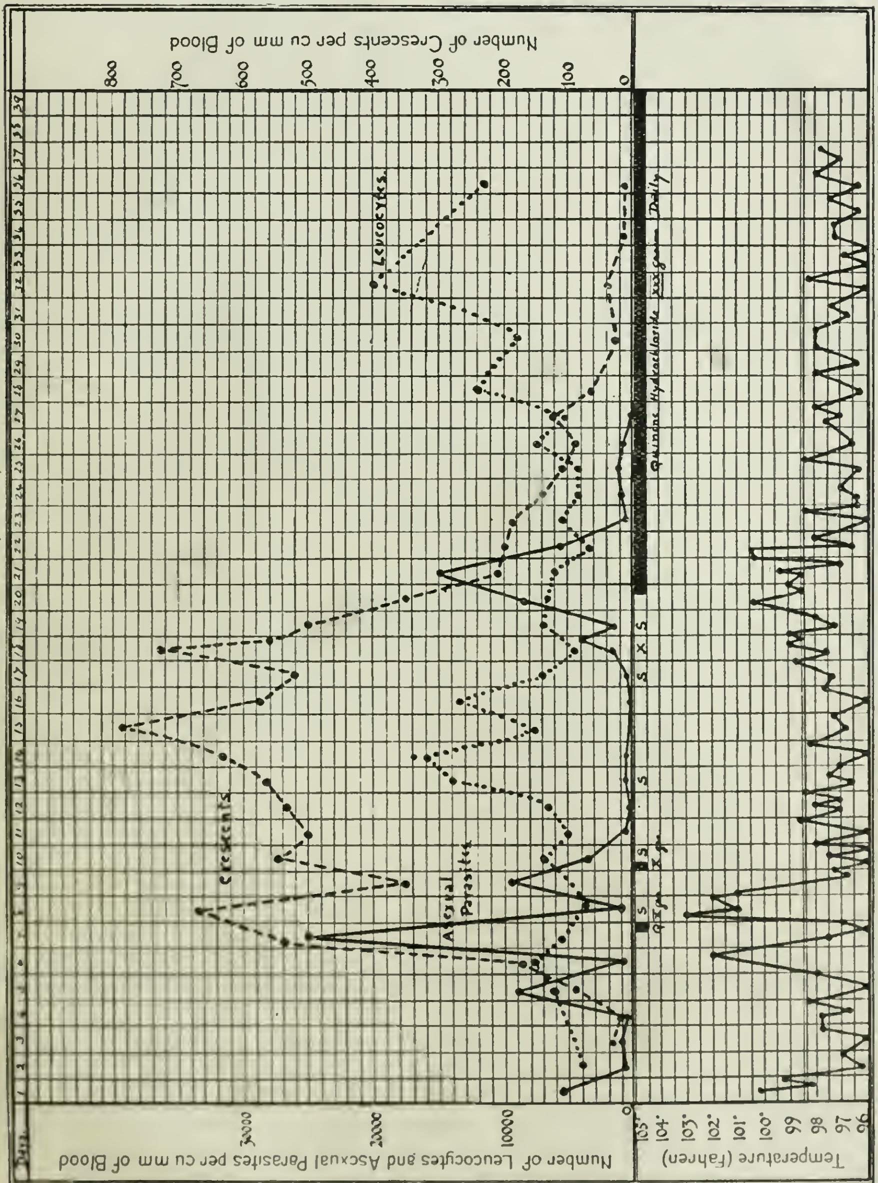


CASE 20.—F.B. *P falciparum.*

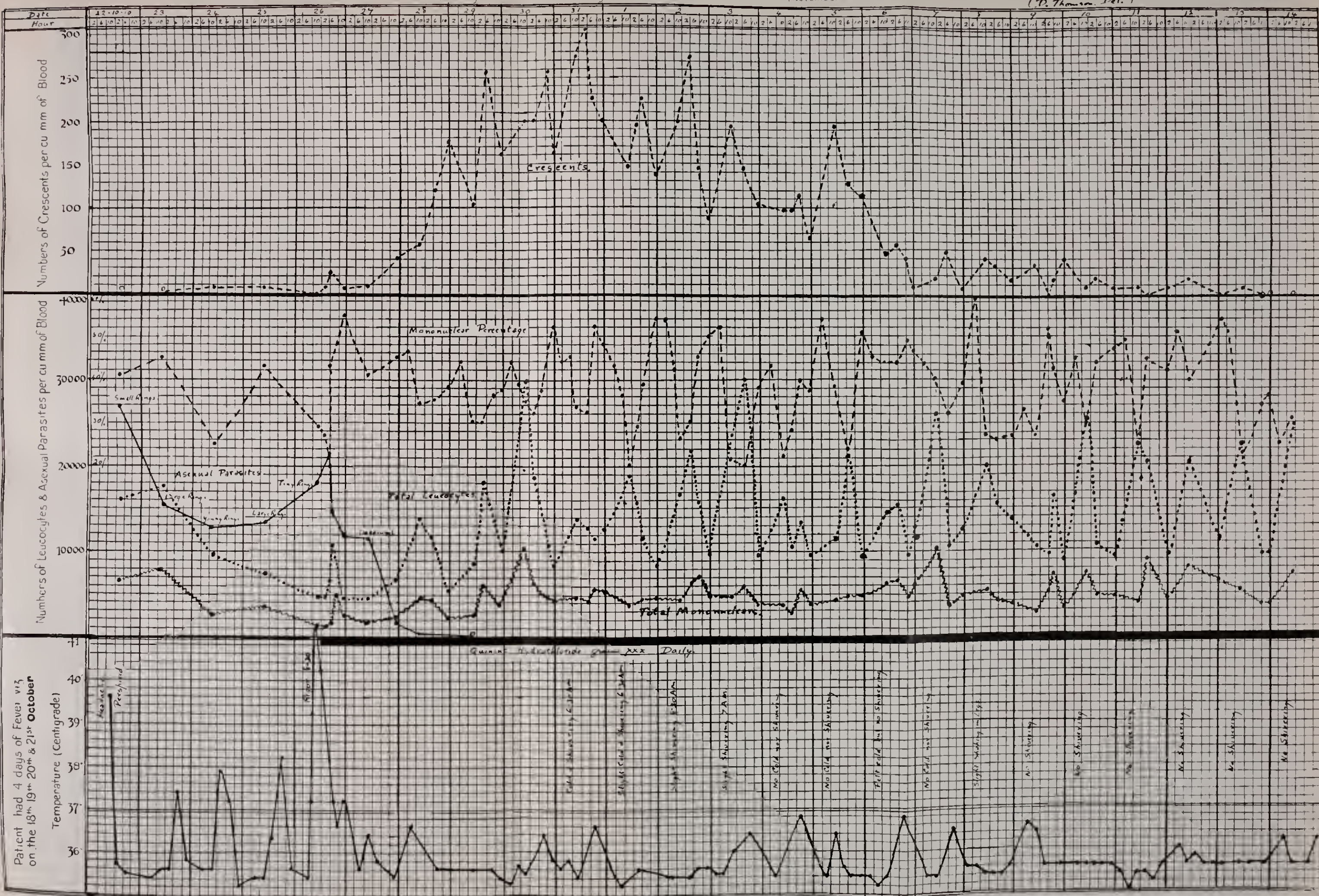


T C. Case 23 (P.falciparum)




J K Case 24 (P falciparum)
Days
Number of Leucocytes and Asexual Parasites per cu mm of Blood
Number of Crescents per cu mm of Blood
Temperature (Fahren)
Crescents
Asexual Parasites
Leucocytes.
Quinine Hydrochloride xxx grains Daily
Temp ——•—— Asexual Parasites (S = Soamin v grains) to X grains ••••••• Leucocytes. (x-x Rays for 20 mins.) over spleen – – –•– – – Crescents
D. Thomson. Del.

C.H. (Malig Tertian Double) Age 25 Case 38



Crescents – – ● – – – ● – – Total Mononuclear Percentage. Total Leucocytes ...●.....●... Total Mononuclear Leucocytes ● ● Assexual Parasites —●——●— Temperature.

G.F Age 68 (Malignant Tertian Malaria) Case 49

